III. Rejections Under 35 U.S.C. §102(e)

A. Martuza '096

Claims 8, 10, 11, 13, 15 and 18-27 stand rejected as anticipated by U.S. Patent 5,585,096 ("Martuza '096"). Applicants respectfully traverse.

The examiner has identified two sections of the Martuza '096 patent that allegedly provide the basis for this rejection. First, the Summary of the Invention states briefly that one may use a herpes simplex virus containing a non-HSV coding sequence to stimulate an anti-tumor immune response in conjunction with radiotherapy. A later cited passage (columns 11-13), however, makes no mention of radiotherapy.

Applicants submit that Martuzza '096, while mentioning a combination of HSV and radiotherapy in passing, falls far short of the kind of teaching necessary to place those of ordinary skill in possession of the invention as now claimed. First, it is not even clear that Martuzza '096 has, in fact, disclosed a combination that even reads on the present invention. Second, and more importantly, it is black letter law that, in order for a reference to anticipate, it must be enabling for the claimed invention.[1] Here, even if Martuzza '096 is deemed to provide literal support for a combination of HSV and radiation, it clearly lacks the kind of detailed disclosure necessary to enable the presently claimed invention. This deficiency is illustrated by reference to the instant application.

The present specification provides a detailed explanation of how to carry out the presently claimed invention. For example, the present specification describes the use of viruses in combination with radiation to create both additive and synergistic responses. It also provides

[1] *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 USPQ 649 (Fed. Cir. 1986) ("[A] §102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it' .... '[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling.'").

an extensive discussion of radiation types and ways to assess the proper exposure to effect therapeutic goals, including various radiation and virus doses for use in combination therapy. Also described are timing issues with respect to when the radiation is provided with respect to the virus therapy. None of these topics is even addressed in Martuzza '096.

In addition, the present disclosure provides examples demonstrating the efficacy of combining radiation and viral therapy. Martuzza '096 contains no relevant examples. While U.S. patents are presumed enabling for what they ***claim***, they are given no more deference on unclaimed embodiments than are any other printed publication. Applicants respectfully submit that if Martuzza '096 were being prosecuted with claims similar to those here, they would certainly be rejected by the examiner on both written description and enablement grounds. With regard to the latter, as stated above, a reference cannot be anticipate if it is not enabling, and there is little doubt that Martuzza '096 fails miserably with regard to this requirement.

B. Martuza '379

Claims 8, 10, 11, 13, 15 and 18-27 stand rejected as anticipated by U.S. Patent 5,585,096 ("Martuza '379"). Again, applicants respectfully traverse.

Much like the Martuza '096 patent, the 'Martuza '379 patent contains only a limited disclosure relating to radiotherapy, and does not teach or suggest a method as claimed here. Rather, Martuza '096 teaches that HSV can be used in an immunization method to protect from HSV infection (see column 6, lines 13-23), which clearly is not a treatment for cancer as

presently claimed.[2] A review of the remainder of the Martuza '379 application did not reveal any other significant mention of radiotherapy.

Again, the present specification provides a categorically different kind of disclosure, with details on types of effects, forms of radiation, doses and timing. It also contains specific examples demonstrating efficacy of the claimed invention. As such, it provides precisely the kind of enabling disclosure that is missing from Martuzza.

Thus, in light of the preceding explanation, applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Rejections Under 35 U.S.C. §103(a)

The examiner has rejected claims 35-55 over U.S. Patent 5,846,945 ("McCormick '945") in view U.S. Patent 5,776,743 ("Frisch '743") and/or Martuza '096 or Martuza '379. According to the examiner, McCormick '945 teaches the use of various mutant oncolytic adenoviruses for killing tumor cells, which adenoviruses may or may not contain an exogenous therapeutic gene, but fails to describe combination therapy with ionizing radiation. The examiner then turns to Martuza '096 and Martuza '379 for the suggestion of combining an oncolytic virus with radiation. Finally, Frisch '743 is cited as teaching that E1A sensitizes tumor cells to radiation. From these teachings, the examiner finds the present claims obvious. Applicants respectfully traverse.

The examiner acknowledges the shortcomings of McCormick '945, and thus the necessity of relying on the secondary references. However, applicants submit that the

[2] All limitations must be considered in coming to a determination of obviousness, and it is an error to ignore specific limitations distinguishing over the references. *In re Saether*, 181 USPQ 35 (CCPA 1974); *In re Glass*, 176 USPQ 489 (CCPA 1973).

combination of either or Martuza '096 or Martuza '379 with McCormick '945 is improper. McCormick '945 deals with adenovirus, whereas Martuza '096 and Martuza '379 deal with herpes simplex virus. These two viruses are distinct in numerous ways, and one of skill in the art would not readily extrapolate from one to the other as the examiner suggests. There simply is no basis on the record to suggest, whatever Martuza '096 and Martuza '379 say about herpes simplex virus, that one of skill in the art could apply those teachings with any predictability to an adenoviral system.[3]

Moreover, as discussed above, Martuza '096 and Martuza '379 both fail to provide an enabling disclosure that would permit one of skill in the art to combine radiation with a viral vector for the purpose of treating cancer. Thus, even if one ***were*** inclined to combine Martuza '096 and Martuza '379 with McCormick '945, applicants submit that the rejection would fail as the combined references would not provide enablement for the presently claimed invention.

Turning to Frisch '743, applicants submit that this reference also is not combinable with McCormick '945. Frisch '743 teaches use of an isolated E1A gene, which is quite inconsistent with the teachings of McCormick, which are directed to use of whole adenoviruses. One must question why, with the availability of infectious adenoviruses, Frisch '743 would propose the isolation of the E1A prior to its introduction into a target cell. In fact, in certain embodiments, the Frisch '743 inventors suggest that the E1A gene be ***introduced into a retroviral vector***, which is capable of integrating into the target cell genome; adenovirus is not capable of such integration. Furthermore, the claims that issued in the Frisch '743 patent are limited to *in vitro* gene transfer, again suggesting the need for tightly controlled transformation conditions. Thus,

[3] Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992).

one of skill in the art, given a reasonable reading of Frisch '743, could only conclude that use of whole adenovirus *in vivo* would not be compatible with the disclosed methods.[4] As such, a combination of Frisch '743 with McCormick '945 is improper as well.

Thus, in conclusion, applicants submit that the examiner has improperly combined the cited references. A suggestion to combine two references must come from the references themselves, not from the examiner. Here, references dealing with (a) herpes simplex virus or (b) an isolated adenoviral gene would not logically be combined with a reference teaching an intact adenovirus. As such, the rejection is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicted. Should Examiner Priebe have any questions regarding this response, a telephone call to the undersigned is invited.

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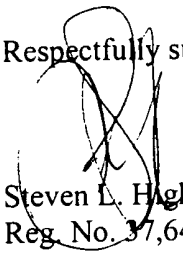
[4] In fact, the teachings of these references appear to conflict, and the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art against the extent to which they discredit another. *In re Young*, 18 USPQ2d 1089 (Fed. Cir. 1991).

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Applicant

FULBRIGHT & JAWORSKI, LLP
600 Congress Ave., Suite 2400
Austin, Texas 78701
(512) 536-3184

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APPENDIX A: MARKED COPY OF CLAIMS

38. (Amended) The method according to claim 46, wherein the tumor [the] cell is located within an animal, and the adenovirus is administered to the animal in a pharmaceutically acceptable form.

55. (Amended) The method of claim [55] 40, wherein said composition comprises from about 10^8 to about 10^{11} adenovirus particles.

APPENDIX B: CLEAN COPY OF PENDING CLAIMS (UNOFFICIAL)

8. The method according to claim 13, wherein the tumor cell is a human tumor cell.

10. The method according to claim 8, wherein the human tumor cell is a brain cancer cell.

11. The method according to claim 8, wherein the human tumor cell is a breast cancer cell.

13. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, a herpes simplex virus and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

15. The method according to claim 13, wherein the herpes simplex virus is HSV-1.

18. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a herpes simplex virus and (ii) ionizing radiation, wherein the combination of herpes simplex virus infection and radiation is more effective than ionizing radiation alone.

19. The method according to claim 18, wherein the composition comprises from about 10^8 to about 10^{10} herpesvirus particles.

20. The method according to claim 18, wherein the administering is by means of an oral or intravenous route.

21. The method according to claim 18, wherein the tumor is brain tumor or breast tumor.

22. The method according to claim 18, wherein the mammal is a human.

23. A method of killing a tumor cell comprising the steps of:

(a) contacting said tumor cell with a herpes simplex virus; and

(b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said herpes simplex virus.

24. The method according to claim 23, wherein the herpes simplex virus is HSV-1.

25. The method according to claim 13, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said herpes simplex virus.

26. The method according to claim 13, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

27. The method according to claim 13, wherein the tumor is a brain tumor or a breast tumor.

35. The method according to claim 46, wherein the tumor cell is a human tumor cell.

36. The method according to claim 35, wherein the human tumor cell is a brain cancer cell.

37. The method according to claim 35, wherein the human tumor cell is a breast cancer cell.

38. The method according to claim 46, wherein the tumor cell is located within an animal, and the adenovirus is administered to the animal in a pharmaceutically acceptable form.

39. The method according to claim 46, wherein the tumor cell is exposed to X-irradiation, γ-irradiation, or β-irradiation.

40. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, an adenovirus lacking an exogenous therapeutic gene and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

41. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a adenovirus lacking an exogenous therapeutic gene and (ii) ionizing radiation, wherein the combination of adenovirus infection and radiation is more effective than ionizing radiation alone.

42. The method according to claim 41, wherein the composition comprises from about 10^8 to about 10^{11} adenovirus particles.

43. The method according to claim 41, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

44. The method according to claim 41, wherein the tumor is brain tumor or breast tumor.

45. The method according to claim 41, wherein the mammal is a human.

46. A method of killing a tumor cell comprising the steps of:

a) contacting said tumor cell with an adenovirus lacking an exogenous therapeutic gene; and

b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said adenovirus.

47. The method according to claim 46, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said adenovirus.

48. The method according to claim 46, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

49. The method according to claim 46, wherein the tumor cell is a brain tumor cell or a breast tumor cell.

50. The method according to claim 46, wherein the composition comprises from about 10^8 to about 10^{11} adenovirus particles.

51. The method of claim 40, wherein said adenovirus is Ad5.

52. The method of claim 41, wherein said adenovirus is Ad5.

53. The method of claim 46, wherein said adenovirus is Ad5.

54. The method of claim 41, wherein said composition is administered intravenously.

55. The method of claim 40, wherein said composition comprises from about 10^8 to about 10^{11} adenovirus particles.